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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,185	06/25/2001	Toshihiko Ashikari	46 221	2199

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EXAMINER
LOEB, BRONWEN

ART UNIT	PAPER NUMBER
1636	8

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,185	ASHIKARI ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 25 June 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

Notice to Comply	Application No.	Applicant(s)	
	09/869,185	ASHIKARI ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The sequences on p. 24, lines 18 and 19 lack SEQ ID Nos. It is unknown if these two sequences are listed computer readable format and paper listing already submitted. If they are already listed in both the CRF and the paper listing, amending the specification to recite the appropriate SEQ ID No. is sufficient to satisfy the sequence compliance rules. However, if these two sequences are not listed, Applicant must provide the items indicated in the following section.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

Part of Paper No. 8

DETAILED ACTION

This action is in response to the application filed 25 June 2001 which included a preliminary amendment to the specification and an Information Disclosure Statement.

Claims 1-8 are pending.

Sequence Compliance

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences were set forth that lack sequence identifiers and it is unknown if they are listed in the computer readable format (CRF) and the paper sequence filed. These sequences include **those on p. 24, lines 18 and 19**. If the Sequence Listing required for the instant application is identical to that of another application, a letter may be submitted requesting transfer of the previously filed sequence information to the instant application. For a sample letter requesting transfer of sequence information, refer to MPEP § 2422.05. Additionally, it is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP § 2422.02).

Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Applicant's attention is drawn to the attached Notice to Comply and the information in Box 7.

2. With regard to the computer readable format filed 25 June 2001, Applicant is informed the Office has corrected a minor problem. Specifically, the date format in

element <141> was corrected to "2001-06-25". Applicant does not need to take any action with respect to this information.

Specification

3. The abstract of the disclosure is objected to because it exceeds 150 words in length. Correction is required. See MPEP § 608.01(b).

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

5. Claim 1 is objected to because of the following informalities: Claim 1 recites an abbreviation "FRT". Abbreviations should be defined at their first use in the claim set. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, first paragraph "Written Description" Requirement published in the Federal Register (Volume 66, Number 4, Pages 1099-1111). Claim 1 is drawn to a DNA construct comprising two FRT sequences of SEQ ID No. 1 or of a sequence substantially identical to that sequence. This is a genus claim in terms of any sequence substantially identical to the FRT sequence of SEQ ID No. 1. The specification mentions SEQ ID No. 1 and several in which there are 5' and 3' deletions (see for instance Fig. 3). This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all sequences based on the teachings in the specification. The specification defines "substantially identical sequences" as one that can be recognized by Flp recombinase to induce recombination, which sequences are obtained by substitution, deletion or addition of one or several nucleotides (p. 10, lines 17-25). There is no discussion of what specific sequences within SEQ ID No. 1 are essential to Flp recognition and recombination induction other than the deletions of the 5' and 3' ends. Therefore, the specification does not describe the claimed substantially identical sequences in such full, clear, concise and exact terms so as to indicate that Applicant has possession of these sequences at the time of filing the present application. Thus, the written description requirement has not been satisfied.

8. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 3-8 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is vague and indefinite in reciting "a DNA fragment" in line 5. Is this the same DNA fragment or different than the one recited in claim 1?

Claim 3 is vague and indefinite in reciting "recombination between a DNA fragment capable of recombining with a yeast chromosomal DNA present in said DNA construct and the yeast chromosomal DNA". This phrase is confusing in that it seems to suggest that the yeast chromosomal DNA is present in the DNA construct. This rejection would be overcome if the claim was amended to recite "recombination between the two DNA fragments in said DNA construct and the yeast chromosomal DNA". This amendment assumes that "a DNA fragment" refers to the same DNA fragment recited in claim 1.

Claim 3 is vague and indefinite in reciting "a selective marker" in line 9. Is this the same selective marker or different than the one recited in claim 1?

Claim 3 is vague and indefinite in reciting "a pair of FRT sequences" in line 12. Is this the same pair of FRT sequences or different than the pair recited in claim 1?

Claim 4 is vague and indefinite in reciting "a DNA construct" in line 2. Is this the same DNA construct or different than the one recited in claim 1?

Claim 4 is vague and indefinite in reciting "a DNA fragment" in lines 3-4. Is this the same DNA fragment or different than the one recited in claim 1?

Claim 4 is vague and indefinite in reciting "an FRT sequence" in line 5. Is this the same FRT sequence or different than the one recited in claim 1?

Claim 4 may be clearer if amended to recite:

> The method of claim 3 wherein said DNA construct further comprises a gene of interest between said DNA fragment and said FRT sequence adjacent to said fragment.

Claim 7 is vague and indefinite because it lacks a method step that clearly refers back to the preamble.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The changes made to 35 U.S.C. §102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. §122(b). Therefore, this application is examined under 35 U.S.C. §102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. §102(e)).

11. Claims 6 and 8 are product-by-process claims. As such, patentability does not rely on the method steps unless the method steps lead to a difference in the product. See MPEP 2113.

12. Claim 8 is rejected under 35 U.S.C. §102(b) as being anticipated by Omura (EP 0 699 748 A2).

Omura teaches the production of beer using a recombinant yeast of the genus Saccharomyces comprising a gene encoding for O-actyl-homoserine sulfhydrylase. The product, beer, is not affected by whether one uses a recombinant yeast obtained using the method of Omura or a recombinant yeast obtained using the instant method. Thus, claim 8 is anticipated by Omura. See entire document.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ashikari et al (EP 0 814 165 A2) in view of Kawahata et al (Yeast (1999) 15:1-10).

Ashikari et al teach a method of constructing recombinant yeast cells which do not contain a selective marker gene. The method employs a vector comprising an R gene and an expressible selective marker wherein the R gene and the selective marker are flanked by a pair of R sensitive sequences oriented in the same direction wherein the R sensitive sequence located nearest the R gene lacks 10 or less nucleotides at the end distal from the spacer sequence in the inverted repeat which is at the opposite end from the end adjacent to said R gene and the R sensitive sequence locates nearest the selective marker gene lacks 10 or less nucleotide sequences at the end distal from the spacer seqence in the inverted repeat which is at the opposite end from the end adjacent to said selective marker gene. The vector further comprises sequences at either end of the above construct wherein the sequences are recombinable with the yeast chromosome. The vector may further comprise a foreign gene to be inserted into the yeast chromosome such that after the recombination event between the pair of R sensitive sequences, the R gene and the selective marker are excised from the chromosome while the foreign gene remains. See entire document, especially pp. 4-5.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to use the FRT/Flp recombination system of yeast in the vector and method taught by Askikari et al. One of ordinary skill in the art would have been motivated to do so because Askikari et al teach the equivalence of the four known site-specific recombination systems (2 element systems in which the recombination sites

comprise inverted repeats separated by a spacer sequence which determines orientation). See p. 2, lines 31-37. It is prima facie obvious to use a known equivalent for the same purpose. See MPEP 2144.06. Furthermore, it would be advantageous as the FRT/Flp recombination system is endogenous to Saccharomyces thus one would not need to incorporate the Flp recombinase gene into the vector.

It would also have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a galactose-inducible growth inhibitory sequence into the vector taught by Askikari et al. One of ordinary skill in the art would have been motivated to do so because Kawahata et al teach the advantage of using such a sequence in marker gene recycling is that is serves as a positive selection for the loss of integrated DNA sequences. Selections, rather than screens, are greatly advantageous in saving time and labor in identifying desired recombinants. Furthermore, Ashikari et al teach one advantage of their vector and method is that it permits the same selective marker may be used for multiple insertions (in other words, marker gene recycling). Success would have been expected by one of ordinary skill in the art for the combined teachings of Ashikari et al in view of Kawahata et al.

16. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ashikari et al in view of Kawahata et al as applied to claims 1-6 above, and further in view of Omura. Ashikari et al in view of Kawahata et al do not teach using the recombinant yeast obtained by their method of transformation in a method to produce beer, or the beer so produced. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to make a recombinant yeast using the vector

and method of Ashikari et al in view of Kawahata et al and use it in a method to produce beer. One of ordinary skill in the art would have been motivated to do so because Omura teach a particular recombinant yeast strain which yields an improved beer and by using the recombinant yeast of Askikari et al in view of Kawahata et al, there would not be any selective markers (such as ampicillin resistance gene or G418 resistance gene) in the transformant. This is advantageous because it reduces the chance of unintentional recombination events leading to pathogenic wild-type yeast containing either or both resistance genes. Success would have been expected as Ashikari et al demonstrate that their method works in brewer's yeast. See p. 10, line 17- p. 11, line 1.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,965,444 in view of Kawahata et al. U. S. Patent No. 5,965,444 claims priority to the same

Japanese patent as EP 0 814 165 and appears to contain an identical disclosure as EP o 814 165. Therefore, the rationale for this rejection is the same as that set forth above in the rejection under 35 USC §103(a).

Conclusion

Claims 1-8 are rejected.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Tracey Johnson, Patent Analyst whose telephone number is (703) 305-2982.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

May 19, 2002

Remy Yucel

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
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